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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,417	08/14/2002	Rainer H Muller	668-59190	8775

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,417	MULLER ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 22-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims:

Claims 1-20 and 22-45 are pending in the application.

Claims 30, and 31 are currently amended.

Claims 44, and 45 are new.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are rejected under 35 USC l02(b) as anticipated by Muller et al (US 5, 858, 410).

Muller et al (Patent '410) teaches a method for preparing nanoparticles of drugs (e.g. corticoids such as prednisolone (see col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are anticipated by '4 10.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 and 22-45 are rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al (WO 98/14174).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water. The drug is dissolved in an organic solvent (page 17, lines I 5-25),. a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization (page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation, WO t 174 discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lines 1-16 ; page 10, lines 24 and page 20, lines 30-35). According to Desai, the drug particles can be in crystalline or amorphous for (page 13, lines 5-10): details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug

particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.
one of ordinary skill in the art would be motivated to make paclitaxel or itraconazole compositions according to the methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products. One of ordinary skill would expect to obtain economic advantage of making stable aqueous suspensions of water-insoluble drug such as paclitaxel in ready-to-use formulation while maintaining low toxicity of the drug in humans. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Claims 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (WO 98/14174) in view of Chen et al US 5104674 (hereinafter Chen).

Chen discloses provision of aqueous dispersions of insolubilized, microfragmented polysaccharide/protein complexes dispersions. Chen teaches an anhydrous dextrose or dried corn syrup (col. 41, lines 36-45). He also teaches a mixture is cold homogenized using a single-piston homogenizer (example 15)
Accordingly, it would have been obvious to one skilled in the art at the time the invention was made to use a piston homogenizer which provides conditions of intense shear, to fragment the solid complex particles (col. 6, lines 59, and 60).

Response to Arguments

2. Applicant's arguments filed 12/12/05 have been fully considered but they are not persuasive. Applicant argues that:

The Examiner cites the abstract and col. 20, lines 23-30 of Muller. However, this disclosure does not anticipate the present invention for the reason that Muller is also a named inventor of the present invention.

In response to this argument, the form paragraph of 102 (b) rejection states that "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States". The statement does not exclude any art owned by the same inventor since there is a one-year period prior to the filing date. Applicant also argues that:

When one introduces a compound into a solvent, -as the word solvent says- the compound would dissolve, and not be in the form of small particles any more. Thus the process of claim 38 of Muller as it is worded will not yield in nanosized particulate carrier particles.

In response to this argument, in claim 38, Muller recites a drug that is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents. The disclosure is clear in the sense of forming a dispersion when the particles are added to water or solvent (a solvent is a medium where a solute should dissolve). In addition, the applicant contends that the active compound dispersed in a solvent to high pressure homogenization, the compound would dissolve and not be in the form of small particles any more is not acceptable because as known in science a dispersion is a mixture in which fine particles of one substance are scattered throughout another substance and a dispersion is classed as suspension, colloid or solution. Generally, the

particles in a solution are of molecular or ionic size; those in a colloid are larger but too small to be observed with an ordinary microscope; those in a suspension can be observed under a microscope or with the naked eye. A coarse mixture (e.g., sand mixed with sugar) is usually not thought of as a dispersion. Please see: (Brown, Theodore. LeMay, Eugen. Bursten, Bruce. Chemistry, The Central Science. 1994 New Jersey: Prentice-Hall, Inc. pages 476, and 477).

This makes the response explicit as the applicant proceeds that the instant active ingredient is dispersed in a non-solvent, which results in a suspension –(the examiner explains that: a suspension is considered one of the forms of a dispersion)- in general it would lead to the same result if a sparingly-soluble substance is dispersed in a solvent or if an ingredient is dispersed in a non-solvent, in the two cases the end-result is a dispersion.

Applicant argues that:

Desai disruption of large droplets of a liquid requires "relatively" low forces (compared to disrupting solids) and appears feasible. From the desai disclosure one would not be motivated to process solid drugs using the same process.

In response, the examiner cites pages 4, 6 where Desai states that high shear is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active. He also states that in a high-pressure homogenizer at a pressure in the range of about 3,000 up to 30,000 psi. Optionally, the organic and/or aqueous phases are thereafter removed from the mixture after having been subjected to high shear conditions.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nabila Ebrahim 3/16/06

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER